CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

BLA:	103949
Submission Dates:	6/10/08
Brand Name	PegIntron® plus Rebetol®
Generic Name:	Peginterferon alfa-2b plus ribavirin
Submission Type:	Priority
Applicant:	Schering-Plough
Reviewer:	Jenny H. Zheng, Ph.D.
PM Secondary Reviewer:	Pravin Jadhav, Ph.D.
Team Leader:	Kellie Reynolds, Pharm.D.
OCP Division:	DCP4
OND Division:	DAVP
Formulation:	Approved PegIntron® for subcutaneous injection and Rebetol® oral solutions or capsule
Indication:	Chronic hepatitis C virus
Population:	Pediatric patients aged ≥3 years with chronic hepatitis C

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I. EXECUTIVE SUMMARY

A. Recommendation

The Office of Clinical Pharmacology has reviewed the information submitted to BLA103949. The information provided in this pediatric BLA were adequate to support the proposed body surface area based dosing of PegIntron® (60 μg/m^2/week administered subcutaneously) in combination with the body weight based REBETOL® (15 mg/kg/day divided in two doses administered orally) in pediatric patients at least 3 years old with chronic hepatitis C.

B. Phase IV Commitments:

None.

C. Summary of Clinical Pharmacology Findings

PegIntron® (PEG2b) is currently indicated for use alone or in combination with ribavirin for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age. The approved PEG2b dose is approximately 1.5 µg/kg once weekly when combined with ribavirin. The approved ribavirin adult doses are 800 to 1400 mg/day (divided in two doses) based on patient's body weight.

Ribavirin is approved in pediatric patients 3 years of age and older in combination with INTRON A (interferon alfa-2b) for the treatment of chronic hepatitis C. The approved pediatric dose is 15 mg/kg/day divided in two doses.

P02538 is a clinical study of PEG2b + ribavirin in pediatric subjects 3 to 17 years of age with compensated chronic hepatitis C. The results indicated that the overall sustained virologic response (SVR, primary efficacy endpoint) was similar or slightly higher than that achieved in the adult pivotal trial as well as in the current standard of care for pediatric patients, Intron A and ribavirin. PEG2b plus ribavirin has been shown to be more efficacious than interferon alfa-2b plus ribavirin in adults at approved doses. Therefore, the pediatric efficacy data are consistent with the observation in adults. The safety profile in this study was consistent with that previously observed with PEG2b/ribavirin in adults and with Intron A/ribavirin in children. The only adverse events in pediatric subjects that were not observed in adults are weight loss and growth inhibition, but these adverse events were seen for Intron A. The safety is determined to be acceptable by the Medical Officer.

Sparse pharmacokinetic (PK) samples as well as limited dense PK samples were collected from Study P02538. The population PK analysis was conducted. The results show

- The body surface area normalized apparent clearance of PEG2b was similar across the pediatric age group (3 through 17 years)
- The PEG2b AUC with the proposed dose of 60 µg/m^2/week administered subcutaneously to pediatric subjects is approximately 50% higher than the values observed with the approved adult dose. However, the safety data from the pediatric subjects support the proposed dose in pediatric subjects.
- The body weight normalized apparent clearance of ribavirin was similar across the pediatric age group (3 through 17 years)
- The ribavirin AUC with the dose of 15 mg/kg/day divided in two doses administered orally to pediatric subjects is similar to the values observed with the approved adult dose and the values previously reported in pediatric patients in combination with Intron A at approved dose.

The following proposed dosing regimens in combination for pediatric patients are acceptable:

- PEG2b: 60 µg/m^2/week subcutaneously
- Ribavirin: 15 mg/kg/day divided in two doses, taken orally

II. QUESTION BASED REVIEW (QBR)

A. General Attributes

A1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

The formulations of peginterferon alfa-2b (PEG2b) and ribavirin being used for pediatric subjects have been approved.

The approved PEG2b formulation is powder for injection, using PegIntron™ REDIPEN® single-dose delivery system. Following reconstitution, each REDIPEN® contains PegIntron™ at strengths of either 50 µg/0.5 mL, 80 µg/0.5 mL, 120 µg/0.5 mL, or 150 µg/0.5 mL

The approved ribavirin formulations are 200 mg capsule and 40 mg/mL oral solution.

Please refer to previous Clinical Pharmacology BLA reviews for PEG2b and NDA reviews for ribavirin.

A2. What is the proposed mechanism of drug action?

The biological activity of PEG2b is derived from its interferon alfa-2b moiety. Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface and initiate a complex sequence of intracellular events. These events include the induction of certain enzymes, suppression of cell proliferation, immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells. Interferon alfa upregulates the Th1 T-helper cell subset in *in vitro* studies. The clinical relevance of these findings is not known.

The mechanisms of inhibition of hepatitis C virus (HCV) RNA by combination therapy with ribavirin and interferon products have not been established.

A3. What is the proposed therapeutic indication?

PEG2b is currently indicated for use alone or in combination with ribavirin for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age.

Ribavirin is approved in pediatric patients 3 years of age and older in combination with INTRON A (interferon alfa-2b) for the treatment of chronic hepatitis C. The approved pediatric dose is 15 mg/kg/day divided in two doses.

The applicant proposes to extend the indication of PEG2b in combination with ribavirin down to 3 years of age for the treatment of chronic hepatitis C in patients with compensated liver disease.

A4. What is the proposed dosage and route of administration?

Adult dosage:

Table 1 shows the approved PegIntron (PEG2b, approximately 1.5 µg/kg once weekly) and Rebetol (ribavirin) dosing in the combination therapy in adults. PEG2b is administered subcutaneously once a week and ribavirin is administered orally twice daily (divided dose AM and PM).

Table 1 Recommended PegIntron Combination Therapy Dosing (Adults)

Body weight kg (lbs)	PegIntron REDIPEN® or Vial Strength to Use	Amount of PegIntron (µg) to Administer	Volume (mL)* of PegIntron to Administer	REBETOL Daily Dose	REBETOL Number of Capsules
<40 (<87)	50 µg per 0.5 mL	50	0.5	800 mg/day	2 x 200-mg capsules A.M. 2 x 200-mg capsules P.M.
40 – 50 (87 – 111)	80 µg per 0.5 mL	64	0.4	800 mg/day	2 x 200-mg capsules A.M. 2 x 200-mg capsules P.M.
51 – 60 (112 – 133)		80	0.5	800 mg/day	2 x 200-mg capsules A.M. 2 x 200-mg capsules P.M.
61 – 65 (134 – 144)	120 µg per 0.5 mL	96	0.4	800 mg/day	2 x 200-mg capsules A.M. 2 x 200-mg capsules P.M.
66 – 75 (145 – 166)		96	0.4	1000 mg/day	2 x 200-mg capsules A.M. 3 x 200-mg capsules P.M.
76 – 85 (167 – 188)		120	0.5	1000 mg/day	2 x 200-mg capsules A.M. 3 x 200-mg capsules P.M.
86 – 105 (189 – 231)	150 µg per 0.5 mL	150	0.5	1200 mg/day	3 x 200-mg capsules A.M. 3 x 200-mg capsules P.M.
>105 (>231)				1400 mg/day	3 x 200-mg capsules A.M. 4 x 200-mg capsules P.M.

* When reconstituted as directed.

Pediatric dosage:

For pediatrics, the approved dose of ribavirin is 15 mg/kg per day orally (divided dose AM and PM) in combination with Intron A.

In this submission, the applicant's proposed dosing for pediatric patients at least 3 years old is determined by body surface area for PEG2b and by body weight for ribavirin. The proposed dose for PEG2b is 60 µg/m^2/week subcutaneously, and 15 mg/kg/day orally for ribavirin in two divided doses. For subjects weighing <47 kg oral solution should be provided, and for subjects weighing ≥47 kg either oral solution or capsules may be given depending on ability to swallow capsules. Table 2 lists the number of capsules used in the protocol for different body weight. The weight cutoff is slightly different from the approved weight cutoff for adults when ribavirin is combined with PEG2b, but because this regimen was studied in P02538, it should be recommended in the label.

Table 2 Recommended Number of Capsules for REBETOL in Combination Therapy (Pediatrics)

Body weight kg (lbs)	REBETOL Daily Dose	REBETOL Number of Capsules
47 – 59 (103-131)	800 mg/day	2 x 200-mg capsules A.M. 2 x 200-mg capsules P.M.
60 – 73 (132-162)	1000 mg/day	2 x 200-mg capsules A.M. 3 x 200-mg capsules P.M.
>73 (>162)	1200 mg/day	3 x 200-mg capsules A.M. 3 x 200-mg capsules P.M.

The reviewer agrees with the applicant proposed PEG2b and ribavirin doses when PEG2b and ribavirin are used in combination in pediatric patients at least 3 years old with chronic hepatitis C. See questions B6 and B7 for details.

A5. What efficacy and safety information contribute to the assessment of clinical pharmacology study data?

The efficacy and safety in pediatric subjects were evaluated in the following study.

P02538: *Assessment of the safety, efficacy, tolerability, and pharmacokinetics of peginterferon Alfa-2b (SCH 54031; PEG2b) plus ribavirin (SCH 18908) in pediatric patients with chronic hepatitis C*

- Age range: 3-17 years
  - Group 1 (n=67): 3-11 years old
  - Group 2 (n=40): 12-17 years old
- Study duration:
  - 48 weeks: HCV Genotypes 1, 4, 5, 6, or high-viral-load (≥600,000 IU/mL) Genotype 3
  - 24 weeks: HCV Genotype 2 or low-viral-load (≥600,000 IU/mL) Genotype 3
- Dose and administration route:
  - PEG2b 60 μg/m^2 by subcutaneous injection once weekly, plus
  - ribavirin 15 mg/kg/day orally in two divided doses (subjects weighing less than 47 kg received ribavirin oral solution, weighing at least 47 kg received capsules or oral solution if they could not take capsules)
- Efficacy:
  - The overall sustained virologic response (SVR, primary efficacy endpoint) was 65%, slightly higher than that achieved in the adult pivotal trial (52%,

study C/I98-580) as well as in the current standard of care for pediatric patients, Intron A and ribavirin (46%, study P00321).
    - Response rate in HCV genotype 1 and HCV genotype 2/3 pediatric subjects were 51.4% and 93%, respectively, as compared to 41% and 75% in adults.
- Safety:
    - The safety profile in this study was consistent with that previously observed with PEG2b/ribavirin in adults and with Intron A/ribavirin in children.
    - The only new adverse events in pediatrics are weight loss and growth inhibition.

Interferon alfa-2b (Intron A) plus ribavirin has been shown to be safe and effective in adult and pediatric populations infected with chronic hepatitis C. However, PEG2b plus ribavirin has been shown to be even more efficacious than interferon alfa-2b plus ribavirin in adults at approved doses.

B. General Clinical Pharmacology

B1. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

In adults, primary endpoint was the proportion of subjects with sustained virologic response (SVR), defined as undetectable HCV-RNA 24 weeks following end of treatment. Although, it is unknown if the disease course of chronic hepatitis C in pediatric patients is similar to that of adults, the primary safety and efficacy parameters measured in adults are also measured in pediatric patients to evaluate the clinical course of chronic hepatitis C (CHC).

B2. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

The exposure-response relationships for efficacy and safety of PEG2b or ribavirin in adults have not been well characterized. The highest PEG2b dose that has been evaluated is 2µg/kg/wk in adults, and the highest ribavirin dose that has been evaluated and approved is 1400 mg/day in adults at least 105 kg.

Jen, F et. al (2001) from Schering-Plough found there was no significant correlation between pharmacokinetic parameters of PEG2b and antiviral response when they evaluated PEG2b (without ribavirin) at doses of 0.5, 1.0, and 1.5 µg/kg/wk. However, a study for another Peg-interferon, peg-interferon-alfa-2a, in combination with ribavirin shows the probability of attaining an SVR in HCV genotypes 1 and 4 was more than 3 to 4 times higher in patients with peg-interferon-alfa-2a levels above the selected cutoff point (Lopez-Cortes, LF et. al, 2008). It is not clear if these analyses were reviewed by the Agency.

In an adult study (C96-114), a dose-response relationship was observed for ribavirin with changes in HCV-RNA at doses between 400 and 1200 mg/day in adults. The largest decrease in HCV RNA was observed at ribavirin 1000-1200 mg/day. Increased ribavirin concentrations have been associated with increased anemia.

In a previous pediatric study of ribavirin in combination with Intron A (Study P00018), 3 different mg/kg doses of ribavirin (8, 12 and 15 mg/kg/day, divided as two daily doses) were studied. Among the three dose groups, decreases in hemoglobin were mainly observed at the highest ribavirin dose. Three out of 20 children (15%) who received ribavirin 15 mg/kg required a dose reduction due to anemia. Dose reductions were not required in the other dose groups. Generally, these hematological changes are comparable to those observed with adults (Study C96-114) with ribavirin doses between 400-1200 mg/day. In pediatric patients, HCV-RNA decreases were similar across all dose groups. This is most likely due to the smaller number of evaluable patients in the pediatric study (n=20-21 per dose arm) than in the adult study (n=40-45 per dose arm). HCV-RNA and hemoglobin changes were similar after week 4 of treatments.

In the current submission, exposure-response relationships for PEG2b and ribavirin were not evaluated.

B3. Are the pharmacokinetics of PEG2b dose-proportional?

In adults, after 4 weeks of once weekly administration, the change in PEG2b exposure (AUC and Cmax) is greater than dose-proportional with increasing PEG2b dose level from 0.5 µg/kg to 2.0 µg/kg.

In children, PEG2b dose proportionality has not been explored.

B4. Are the pharmacokinetics of ribavirin dose-proportional?

In adults, following single doses of ribavirin (400, 800 and 1200 mg), AUC was dose proportional, whereas C_{max} was less than dose proportional.

In children, the mean exposure data of ribavirin suggested dose proportionality over 8, 12, and 15 mg/kg. However, individual data suggest that the 12 mg/kg and 15 mg/kg doses provide a comparable range of exposures, because the pharmacokinetics of ribavirin are generally variable. See Dr. Jooran Kim's previous Clinical Pharmacology Review for ribavirin pediatric supplement in combination with Intron A (NDA 20903, SE8-013, submitted: 2/28/2001).

B5. Do PK parameters change with time following chronic dosing?

For PEG2b, the apparent clearance (CL/F) in adults is decreased from 25.0 mL/hr/kg at Week 1 to 18.5 mL/hr/kg at Week 4 at a dose of 1.5 µg/kg/week. The population pharmacokinetic analysis (Jen, F et. al, 2001) indicated that the apparent clearance continued to decline by 33.7% from Week 4 to Week 48. The predicted CL/F on Week 1 and Week 4 from the analysis were very similar to the values that were observed in other studies that the Agency has reviewed.

In adults, ribavirin pharmacokinetics does not change with time.

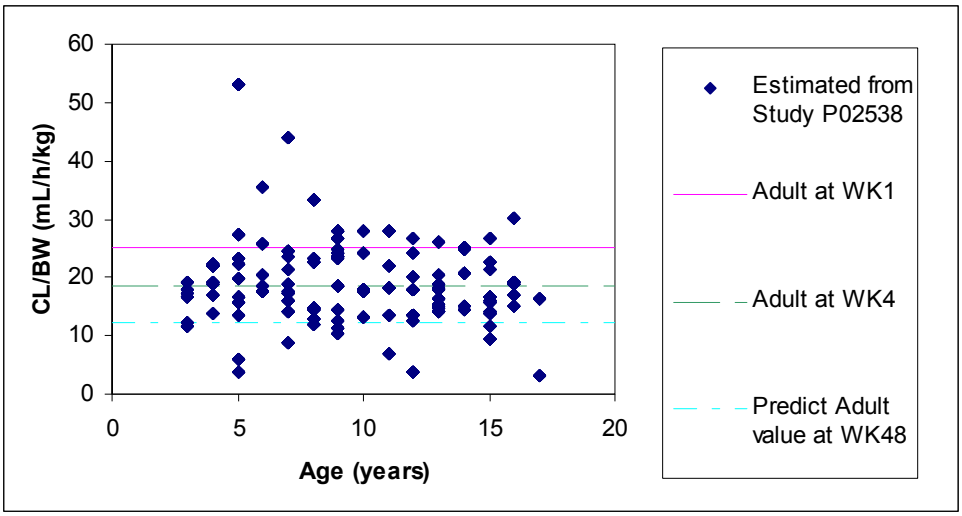
B6. How does the PK of PEG2b in pediatric patients compare to that in adults? Is the proposed dose for PEG2b in pediatric patients appropriate?

The dose of PEG2b used for study P02538, 60 μg/m^2 QW, is approximately equivalent to the dose approved for adults, 1.5 μg/kg QW, based on calculated conversion to body surface area (BSA).

The pharmacokinetics of PEG2b in pediatric subjects were determined by population PK, and were described by a one-compartment model with first-order absorption and first-order elimination based on an assumption of linear PK (CL is not changed with time). In adults, the apparent clearance (CL/F) decreases from 25.0 mL/hr/kg at Week 1 to 18.5 mL/hr/kg at Week 4 at dose of 1.5 μg/kg/week. The population pharmacokinetic analysis (Jen, F et. al, 2001) indicated that the apparent clearance continued to decline by 33.7% from Week 4 to Week 48. In Pediatric Study P02538, the concentrations were measured from Week 1 through Week 48. As indicated in the Pharmacometric Review, the nonlinear model is not expected to change the PK results significantly for pediactric subjects.

Because only body weight normalized clearance was reported for PEG2b in adults, the body weight normalized apparent clearances were estimated in pediatric subjects. As shown in Figure 1, the body weight normalized apparent clearances in pediatric subjects are within the range of the observed values in the adults. Therefore, if the pediatric subjects take the same dose as adults (1.5 μg/kg/week), the PEG2b AUC in pediatric subjects should be similar to the values observed in adults.

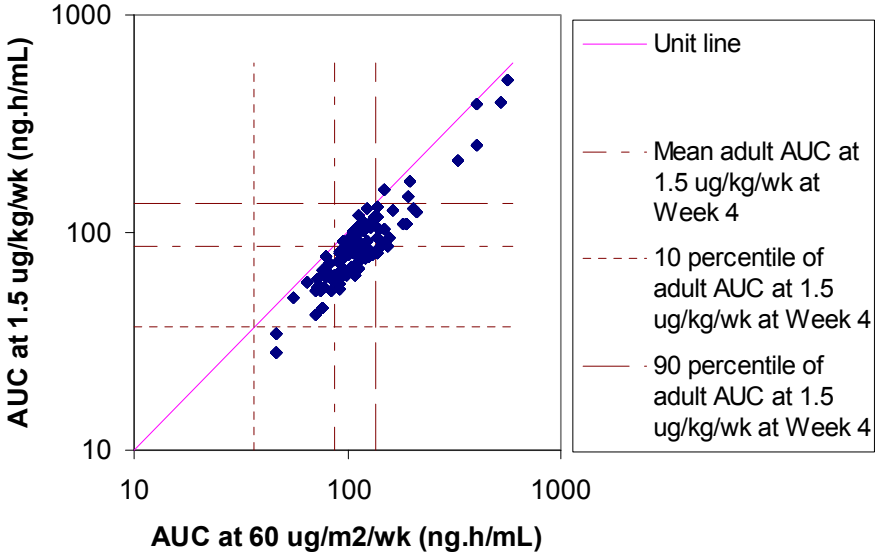
Figure 1: The comparison of body weight normalized apparent clearance of PEG2b between pediatric subjects in Study P02538 and adults from historical data



Because body weight (BW) based regimen is used in adults for PEG2b and is used for both adults and pediatrics for ribavirin; in addition, 1.5 μg/kg/week PEG2b in pediatric subjects may provide similar exposures as compared to the achieved level in adults at approved dose, BW based regimen for PegIntron was also explored to check if it can provide similar exposure as proposed body surface area (BSA) based regimen (the regimen studied in P02538). As shown in Figure 2, the PEG2b AUCs for BW based regimen at 1.5 μg/kg/week are somewhat lower than the values obtained based on the

body surface area (BSA, 60 μg/m^2/week). Only AUC was compared, because the Cmax of PEG2b can not be accurately estimated from the sparse samples in Study P02538.

Figure 2 Predicted PEG2b AUC Correlation between Body Surface Area based or Body Weight Based Regimen (Pediatric Study P02538)



In pediatric subjects receiving BSA based dosing of PEG2b at 60 μg/m^2/week, the log-transformed ratio estimate of exposure during the dosing interval is predicted to be approximately 50% higher than observed in adults receiving 1.5 μg/kg at Week 4 (Table 3). However, because PEG2b exposure increases with time and the exposure collected in this study is from Week 1 to Week 48, the exposure comparison here only serves as a rough comparison. Because BW based regimen at 1.5 μg/kg/week would provide exposure lower than the BSA based regimen at 60 μg/m^2/week, and the efficacy and safety data support the studied BSA based regimen (see QBR A5), a higher BW normalized dose than used in adults should be used to achieve the exposures of 60 μg/m^2/week in pediatric patients. Although BW based regimen may provide simpler regimen than BSA based regimen, the Medical Officer indicated BSA based regimen has been used for interferons for other indications. Therefore, **the applicant's proposed BSA based dosing regimen 60 μg/m^2/week for PEG2b in pediatric patients at least 3 years old is acceptable.**

Table 3 Predicted mean (%CV) AUC(τ) of PEG2b in Pediatric Subjects as compared to adults at Week 4

	PEG2b	
Dose	1.5 µg/kg in Adult Subjects	60 µg/m^2/wk in Pediatric Subjects
Study/Source	P02927 & I95-060	P02538
n	22 [c]	107
AUC(τ) mean (%CV)	71100 (36)	127000 (63)
AUC(τ) LS mean [a]	67700	107000[b]
AUC(τ) Ratio (90% CI): Pediatric vs Adult	1.58 (1.41-1.77) [b]	

CV% = coefficient of variation in percent; n = the number of subjects
AUC(τ) (pg·hr/mL) for PEG2b: τ =168 hr
a: Model-based (least squares) mean: ANOVA extracting the effects due to subject type
b: n=102for P02538. Subjects 7093, 18055, 20030, 22095, 24008 from P02538 were excluded due to statistical outlier; AUC geometric mean is 114500 pg.hr/mL including these 5 subjects
c: n=6 for I95-060 and n=16 for P02927
ANOVA = analysis of variance; CI = confidence interval; LS mean= least-square mean; NA = not applicable

B7. How does the PK of ribavirin in pediatric patients compare to that in adults and the previous study in pediatric patients? Is the proposed dose for ribavirin in pediatric patients appropriate?

The pharmacokinetics of ribavirin in pediatric patients were determined by population pharmacokinetics, and are described by a two-compartment model with first-order absorption and first-order elimination. Body weight was the most important covariate for clearance, distributional clearance, and volume of distribution of central and peripheral compartments. The body weight normalized apparent clearance of ribavirin is similar across the pediatric age groups and similar to those reported in a prior study of ribavirin in combination with Intron A and in adult patients (Figure 3). For pediatric patients, the approved dose of ribavirin is 15 mg/kg per day (divided dose AM and PM) orally in combination with Intron A. As shown in Table 4, the AUCτ of ribavirin in pediatric subjects from Study P02538 and the previous study of ribavirin in combination with Intron A are similar. Therefore, **the applicant's proposed body weight based regimen of ribavirin 15 mg/kg/day is acceptable.**

Figure 3: The comparison of body weight normalized apparent clearance of ribavirin between pediatric subjects in Study P02538 and the values observed in previous pediatric and adult studies

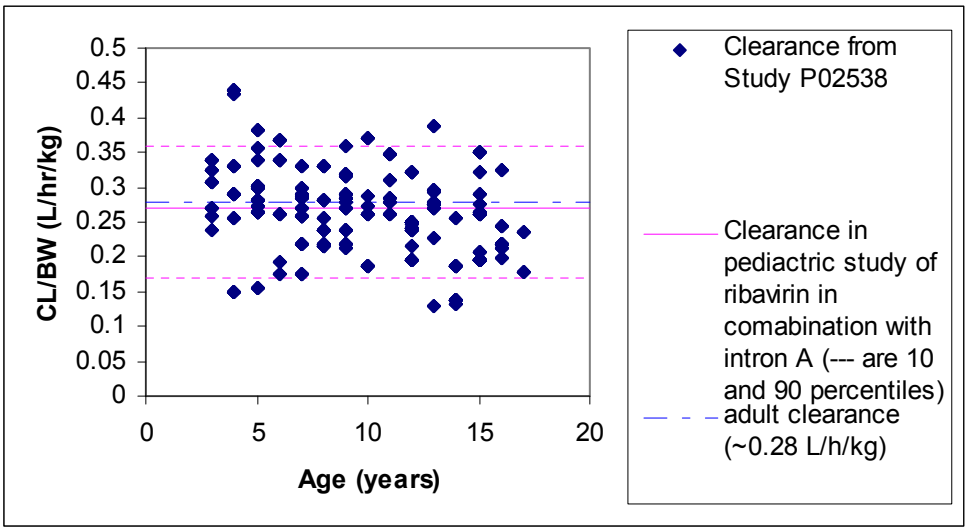


Table 4 Across Study Comparison of mean (%CV) AUC(τ) of ribavirin in Pediatric Subjects

	Ribavirin	
Dose	15 mg/kg/day as 2 divided doses in Pediatric Subjects	
Study/Source	P02538	Product Information
n	107	17
AUC(τ) mean (%CV)	29100 (25)	29774 (26)
AUC(τ) LS mean [a]	28300	NA
AUC(τ) Ratio (90% CI): Pediatric vs Adult	NA	

CV% = coefficient of variation in percent; n = the number of subjects
AUC(τ) (ng·hr/mL) for ribavirin: τ =12 hr
a: Model-based (least squares) mean: ANOVA extracting the effects due to subject type

C. Intrinsic Factors

C1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

In children:

- Apparent clearance of PEG2b increases with age (Figure 4)
- The body surface area (BSA) normalized apparent clearance of PEG2b was generally similar across the pediatric age group (3 through 17 years) (Figure 5)--- **support the proposed BSA based regimen in pediatric patients** (see Question B6 for more details)

Figure 4: The apparent clearance of PEG2b in pediatric subjects increases with age in Study P02538

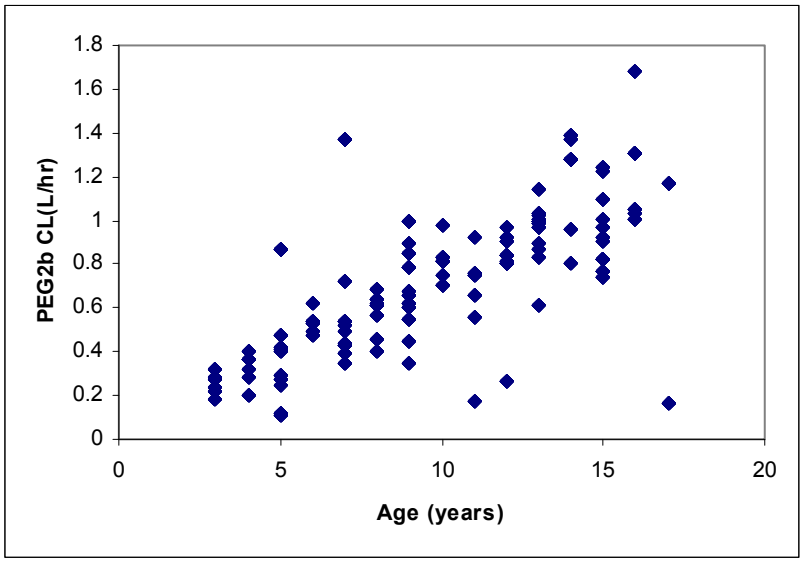
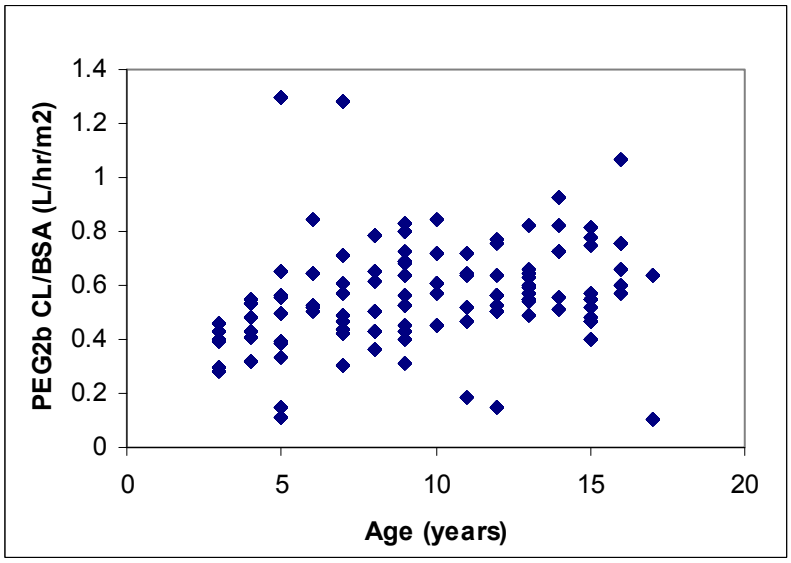
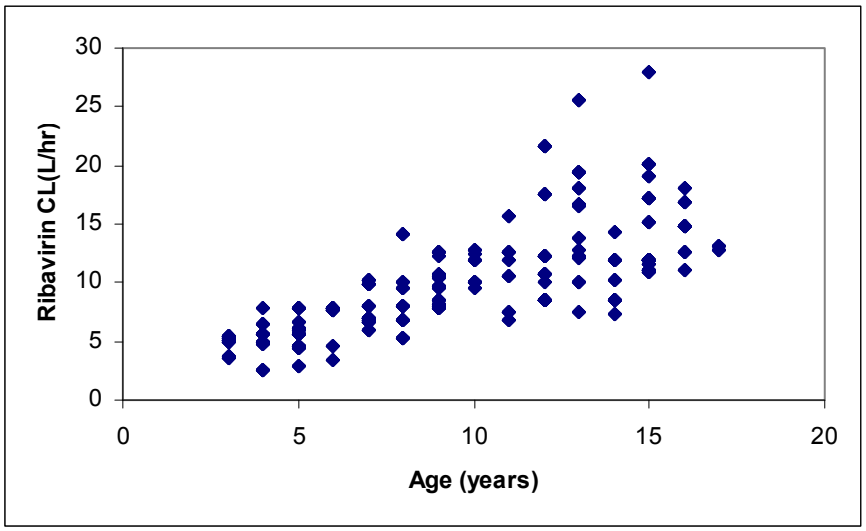


Figure 5: The body surface area normalized apparent clearance of PEG2b in pediatric subjects with age from 3 to 17 years old in Study P02538



- Apparent clearance of ribavirin increases with age (Figure 6).
- The body weight-normalized apparent clearance of ribavirin was similar across the pediatric age group (3 through 17 years)-**support the body weight based regimen in pediatric patients** (see Question B7 for more details).

Figure 6: The apparent clearance of ribavirin in pediatric subjects increases with ages in Study P02538



D. Extrinsic Factors

Extrinsic factors in pediatric patients have not been evaluated in this submission.

E. General Biopharmaceutics

In adults, the bioavailability of ribavirin increased significantly (70%) with food. Ribavirin should be taken with food when combined with PEG2b. In study P02538, ribavirin was administered with food.

F. Analytical Section

Assay methods are acceptable.

III. DETAILED LABELING RECOMMENDATIONS

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IV. PEDIATRIC STUDY CLINICAL PHARMACOKINETIC REVIEW

Title: Part 1: Assessment of the Safety, Efficacy, Tolerability, and Pharmacokinetics of Peginterferon Alfa-2b (SCH 54031; PEG2b) Plus Ribavirin (SCH 18908) in Pediatric Patients with Chronic Hepatitis C (Protocol No. P02538)

Note: Part 2 is the 5-year long-term follow-up portion of the study and is not included in the study report.

Objectives:

- To assess the safety, efficacy, and tolerability of the combination of peginterferon alfa-2b (PEG2b) 60 µg/m2 once weekly (QW) plus ribavirin 15 mg/kg/day in pediatric subjects with chronic hepatitis C (CHC).
- To measure the multiple-dose pharmacokinetics of PEG2b and ribavirin in pediatric subjects with CHC.

Study Design:

- Phase 3/1B open-label, global, multicenter study
- Age range: 3-17 years
    - Group 1 (n=67): 3-11 years old
    - Group 2 (n=40): 12-17 years old
- Study duration (+ 24 weeks post-treatment follow-up):
    - 48 weeks: HCV Genotypes 1, 4, 5, 6, or high-viral-load (≥600,000 IU/mL) Genotype 3
    - 24 weeks: HCV Genotype 2 or low-viral-load (≥600,000 IU/mL) Genotype 3
- Dose and administration route:
    - PEG2b 60 µg/m2 by subcutaneous injection QW, plus
    - ribavirin 15 mg/kg/day orally in two divided doses (subjects weighing less than 47 kg received ribavirin oral solution, others received capsules)

Formulation:

- The approved PEG2b powder for injection, using PegIntron™ REDIPEN® single-dose delivery system. Following reconstitution, each REDIPEN® contains PegIntron™ at strengths of either 50 µg/0.5 mL, 80 µg/0.5 mL, 120 µg/0.5 mL, or 150 µg/0.5 mL
- The approved ribavirin formulations: 200 mg capsule and 40 mg/mL oral solution.

PK Sampling:

- Pharmacokinetic Group (n=21): intensive pharmacokinetic (PK) sampling on Week 1, 4 and 8 for PEG2b, on Week 1 and 4 for ribavirin.

Table 1: PK sampling scheme

Age Group	n[a]	Week	Drug	Schedule[b]			
				1	2	3	4
3-5 yr	12	1	PEG	6, 24 & 96 hr	2, 36 &120 hr	10, 48 & 144 hr	12, 72 &168[c] hr
			REB	0.5, 1& 6 hr	0.5, 2 & 8 hr	1.5, 4 & 10 hr	2, 6 & 12 hr
		4	PEG	0 hr	0 hr	0 hr	0 hr
			REB	0, 0.5, 1 & 6 hr	0, 0.5, 2 & 8 hr	0, 1.5, 4 & 10 hr	0, 2, 6 & 12 hr
				Subjects from Schedules 1 and 3		Subjects from Schedules 2 and 4	
		8	PEG	0, 6,10, 24, 48, 96 & 144 hr		0, 2,12, 36, 72, 120 & 168 hr	

Age Group	n[a]	Week	Drug	Schedule[b]		
				1	2	3
6-11 yr	18	1	PEG	6, 10, 24 & 72 hr	12, 36, 120 & 168 hr	2, 48, 96 &144 hr
			REB	1, 2, 4 & 6 hr	0.5, 1.5, 8, 10 & 12 hr	0.5, 1, 2, 4 & 12 hr
		4	PEG	0 hr	0 hr	0 hr
			REB	0, 1, 2, 4 & 6 hr	0, 0.5, 1.5, 8 & 12 hr	0, 1.5, 4, 8 &10 hr
				All subjects from Schedule 1 plus 50% subjects from Schedule 2		All subjects from Schedule 3 plus 50% subjects from Schedule 2
		8	PEG	0, 2,10, 24, 72, 120 & 168 hr		0, 6, 12, 36, 48, 96 & 144 hr

Age Group	n[a]	Week	Drug	Schedule[b]
12-17 yr	20	1	PEG	0, 2, 6, 10, 12, 24, 36, 48, 72, 96, 120, 144 & 168 hr
			REB	0, 0.5, 1, 1.5, 2, 4, 6, 8, 10 & 12 hr
		4	PEG	0 hr
			REB	0, 0.5, 1, 1.5, 2, 4, 6, 8, 10 & 12 hr
		8	PEG	0, 2, 6, 10, 12, 24, 36, 48, 72, 96, 120, 144 & 168 hr

PEG=PEG-Intron; REB=REBETOL.

a: n=number of children targeted for enrollment in specified age groups.

b: Three to five year olds in the pharmacokinetic study will be enrolled in one of the four schedules above; 6-11 year olds in the pharmacokinetic study will be enrolled in one of the three schedules above; all 12-17 year olds in the pharmacokinetic study will be enrolled in the same schedule as above.

c: One hundred and sixty eight hours is the first day of the next week (ie, Week 2-Day 1) just prior to the PEG-Intron dose.

- Profile Pharmacokinetic Group (n=86): sparse PK sampling on Weeks 4, 6, 12, 24, 30, and 48

Analytical Methodology: Peg-Intron concentrations were measured using a validated electrochemiluminescent (ECL) immunoassay with a limit of quantitation of 40 pg/mL. Ribavirin concentrations were determined using a validated LC-MS/MS method with a limit of quantitation of 50 ng/mL. These methods are acceptable.

Pharmacokinetic Analysis Methods: A nonlinear mixed effects modeling approach was used to analyze the ribavirin and PEG2b data. NONMEM was used in the population pharmacokinetic analysis. The non-compartmental analyses (NCA) for ribavirin and PEG2b were conducted in 6 subjects aged 12-17 years.

Results: Originally only population pharmacokinetic analysis results were submitted. The results are shown in the Pharmacometric Review. The agency has requested the applicant to provide the PK data using non-compartmental analysis (NCA) for 21 subjects who had intensive PK sampling and compare the results with the values estimated from population PK analysis. The applicant indicated in order to decrease the number of blood collections for an individual child, a typical adult blood sampling scheme was divided among multiple children in the 3-5 and 6-11 year old age groups according to the schedule outlined in Table 1 above. Therefore, 15 subjects (3 subjects in 3-5 years, 12 subjects in 6-11 years) had a slightly limited PK profile for Pegintron and ribavirin while the full PK profiles of PegIntron and ribavirin were characterized in 6 subjects aged 12-17 years.

The pharmacokinetic parameters estimated from NCA analysis for ribavirin at Week 4 and PEG2b at Week 8 and from population PK analysis (n=107) at steady state are summarized in Table 2.

Table 2 Mean (%CV) of Predicted PK Parameters of PEG2b and Ribavirin at Steady State in Pediatric Subjects (ages 12 to 17 years old).

PegIntron			
Dose	**60 μg/m²/week**		
Analysis	Pop-PK[c]	Pop-PK[c]	NCA
n	107	6	6
Tmax (hr) [a]	24 (12-36)	24 (18-24)	24 (10-36)
Cmax	1550 (67)	1180 (19)	1430 (33)
AUC(τ)	127000 (63)	102000 (16)	113000 (31)
Ribavirin			
Dose	**15 mg/kg/day as 2 divided doses**		
Analysis	Pop-PK[c]	Pop-PK[c]	NCA
n	107	6	6
Tmax (hr) [a]	1.5 (1.0-3.5) [b]	2.25 (1.5-3.5) [b]	2.0 (1.5-4.0)
Cmax	2840 (22)	3290 (36)	3120 (27)
AUC(τ)	29100 (25)	35500 (36)	29300 (23)

CV% = coefficient of variation in percent; n = the number of subjects

a: Median (range)

b: Ka of ribavirin was fixed at 0.31/hr, based on the value in a published literature[1].

c: Source data: population PK report in P02538 CSR

Cmax (ng/mL) for ribavirin

Cmax (pg/mL) for PegIntron

AUC(τ) (ng.hr/mL) for ribavirin: τ =12 hr

AUC(τ) (pg.hr/mL) for PegIntron: τ =168 hr

Conclusion: In the general, the PK parameters estimated from population PK analysis and from NCA analysis showed good correlations for both PegIntron and ribavirin.

Note: For population PK analysis, see Pharmacometric Review

V. PHARMACOMETRIC REVIEW

Summary of Findings

Key Review Questions

The purpose of this review is to address the following key questions:

Q1: Are the applicant's proposed doses for peginterferon alfa-2b (PEG2b) in pediatric patients supported by the data?

Yes. See QBR B6.

Q2: Are the applicant's proposed doses for ribavirin in pediatric patients supported by the data?

Yes. See QBR B7.

Recommendations

The information provided in this pediatric BLA were adequate to support the proposed body surface area based dosing of PegIntron® (60 µg/m^2/week administered subcutaneously) in combination with the body weight based REBETOL® (15 mg/kg/day divided in two doses administered orally) in pediatric patients at least 3 years old with chronic hepatitis C.

Label Statements

See Detailed Labeling Recommendations.

Pertinent regulatory background

PEG2b is currently indicated for use alone or in combination with ribavirin for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age. The approved PEG2b dose is approximately 1.5 µg/kg once weekly. The approved ribavirin adult doses are 800 to 1400 mg/day (divided in two doses) based on patient's body weight.

Ribavirin is indicated in combination with INTRON A (interferon alfa-2b) for injection for the treatment of chronic hepatitis C in patients 3 years of age and older with compensated liver disease previously untreated with alpha interferon and in patients who have relapsed following alpha interferon therapy. The approved dose in pediatric patients is 15 mg/kg/day divided in two doses.

See QBR for more details

Results of Applicant's Analysis

The applicant conducted a population pharmacokinetic (PopPK) analysis for pediatric subjects aged 3 to 17 years using the data from Study P02538. The pharmacokinetic (PK) parameters obtained from the analysis were compared to the available adult PK and the previous pediatric PK data (only available for ribavirin when combined with Intron A). See Pediatric Study Clinical Pharmacology Review for detailed study design.

A nonlinear mixed effects modeling approach was used to analyze PEG2b and ribavirin data. NONMEM was used in the population pharmacokinetic analysis. The structural model was first explored using intensive data at Week 1, 4 or 8 (pharmacokinetic group: n = 21 subjects). The final population pharmacokinetic analysis was conducted with the pooled available data from all 107 subjects (pharmacokinetic group and profile pharmacokinetic group (sparse sampling)).

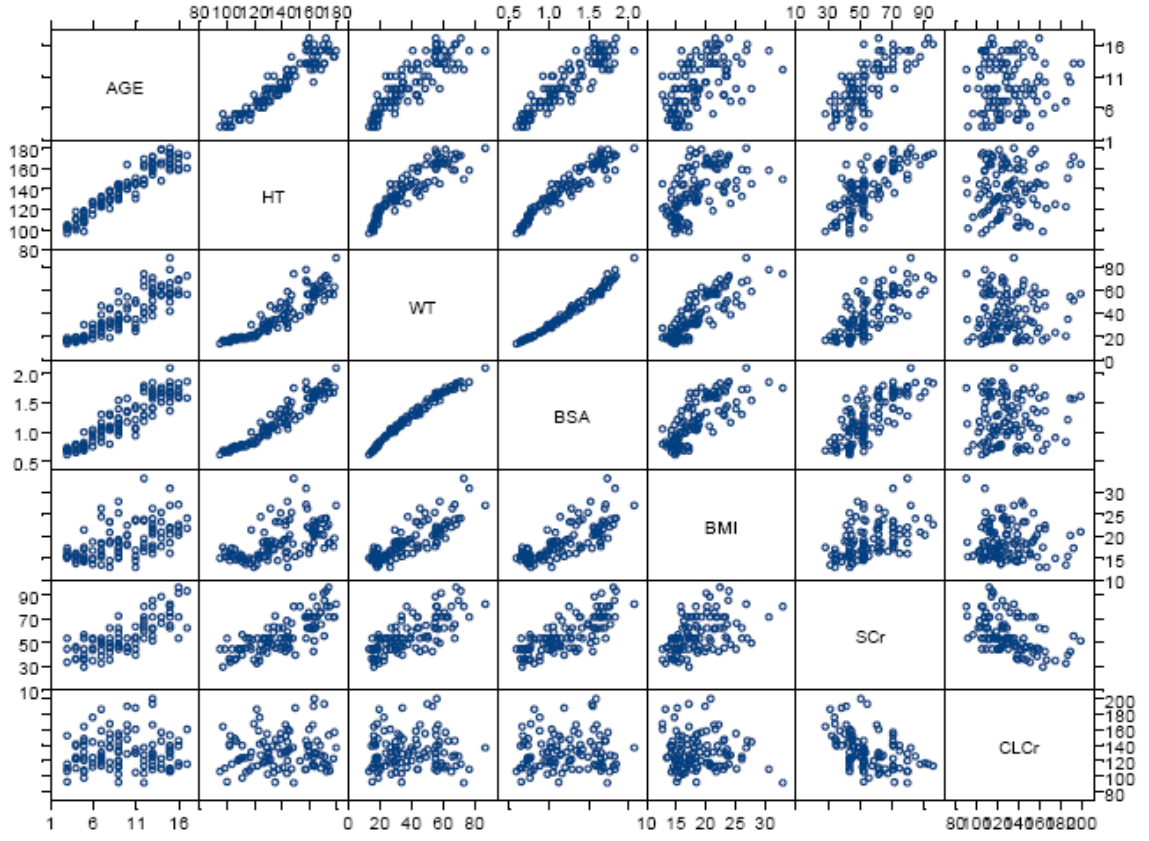
PegIntron

All pediatric subjects who received PEG2b and had at least one measurable PEG2b serum concentration were included in the analysis. Total of 822 serum PEG2b samples were used in the population pharmacokinetic analysis.

A one compartment model with first order absorption and first order elimination was used for Peg-Intron. The apparent clearance (CL/F, where F is bioavailability), apparent volume of distribution (V/F), and first-order absorption rate constant (ka) parameters were estimated. Inter and intra-subject variabilities were estimated.

Covariates were investigated using a two-stage approach or using a stepwise generalized additive modeling (GAM) procedure. The final model included two covariates as significant: age and gender. In current pediatric data sets, size parameters such as body weight, height, BMI and body surface area (BSA), are highly correlated with other development- or maturation related parameters, for example, renal function (serum creatinine (SCr), estimated creatinine clearance (CrCL) by Schwartz formula) or age. The correlation of these parameters is shown in Figure P1.

Figure P1 The Correlation of Demographic Variables, Serum Creatinine, Creatinine Clearance in Pediatric subjects



Goodness-of-fit plots for the final pharmacokinetic model are presented in Figure P2. The individual predicted vs. observed plasma PegIntron concentrations were scattered around the line of unity. The weighted residuals did not show any major trend when plotted over sampling time or population predicted value, suggesting that the model was appropriately unbiased. With the exception of few subjects with higher exposures, the model fits the data well.

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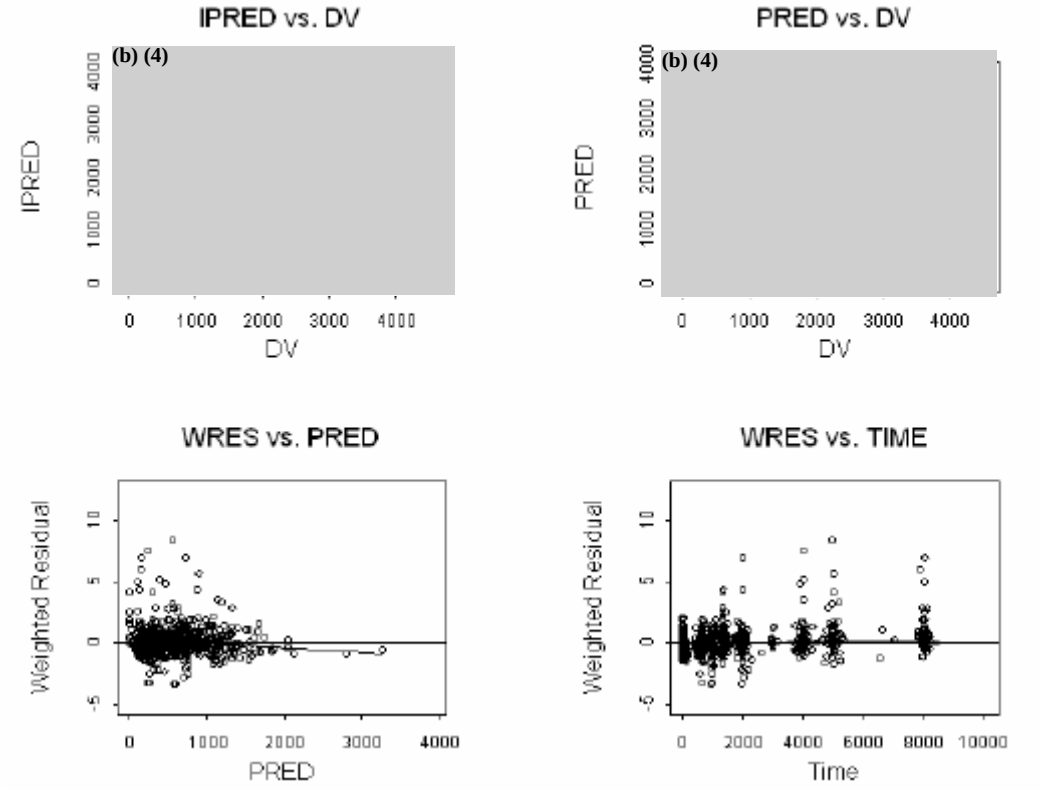
Figure P2: Goodness of Fit Plots for the Final Population Pharmacokinetic Model of Peg-Intron: individual predicted concentrations vs. observed concentrations (upper left); population predicted concentrations vs. observed concentrations (upper right); weighted residuals vs. population predicted concentrations (bottom left); weighted residuals vs. time (bottom right).



IPRED: individual predicted concentration; DV: dependent variable, observed Peg-Intron plasma concentration; PRED: population predicted concentration; WRES: weight residual.
Lines in IPRE vs DV and PRED vs DV plots are lines of unity, and lines in WRES vs PRED and WRES vs TIME plots are loess smooth lines.

The final model is a one compartment model with first order absorption, first-order elimination, exponential inter-individual variabilities on clearance, volume of distribution and with a combination additive and proportional residual error model. The final population pharmacokinetic parameters and estimated effects of the significant covariates on CL/F and V/F estimate of PegIntron are included in Table P1.

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Table P1 Population Pharmacokinetic Parameter Estimates for Peg-Intron

Parameters	Estimate (%SE)	Inter-individual variability (%SE)
CL/F (L/hr)	0.626 (10)	47.0% (39)
V/F (L)	51.4 (16)	67.5% (36)
Ka (1/hr)	0.0909 (16)	24.4% (150)
Covariates	**Estimated Effect (%SE)**	
Age on CL/F	1.10 (18)	
Sex on CL/F	1.27 (16)	
Age on V/F	1.46 (15)	

Residual variability		
Proportional error	40.6% (20)	
Additive error (pg/mL)	116 (31)	

CL/F = apparent clearance; Ka = first order absorption rate constant; SE = standard error; V/F = apparent volume of distribution.

Because most of concentration measurements used in the analysis of PegIntron were from sparse PK sampling, the concentrations may not contain enough information to estimate first order absorption rate constant (Ka) accurately for each individual. The estimated standard error (SE) of inter-individual variability for Ka was greater than SE for CL/F and V/F.

The CL/F in female subjects, was appeared approximately 27% higher than in male subjects of the same age. However, this may be influenced by a few subjects who appeared as outliers. Figure P3 shows that the estimated apparent volume of distribution (V/F) (final model estimates). The estimated volume of distribution for the Subjects 7093 and 22095 is much larger than that of other subjects and appeared as outliers, thus pharmacokinetic parameters were reestimated using the data excluding these two subjects.

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Figure P3 Subjects 7093 and 22095 appears to be outliers in the V/F estimate

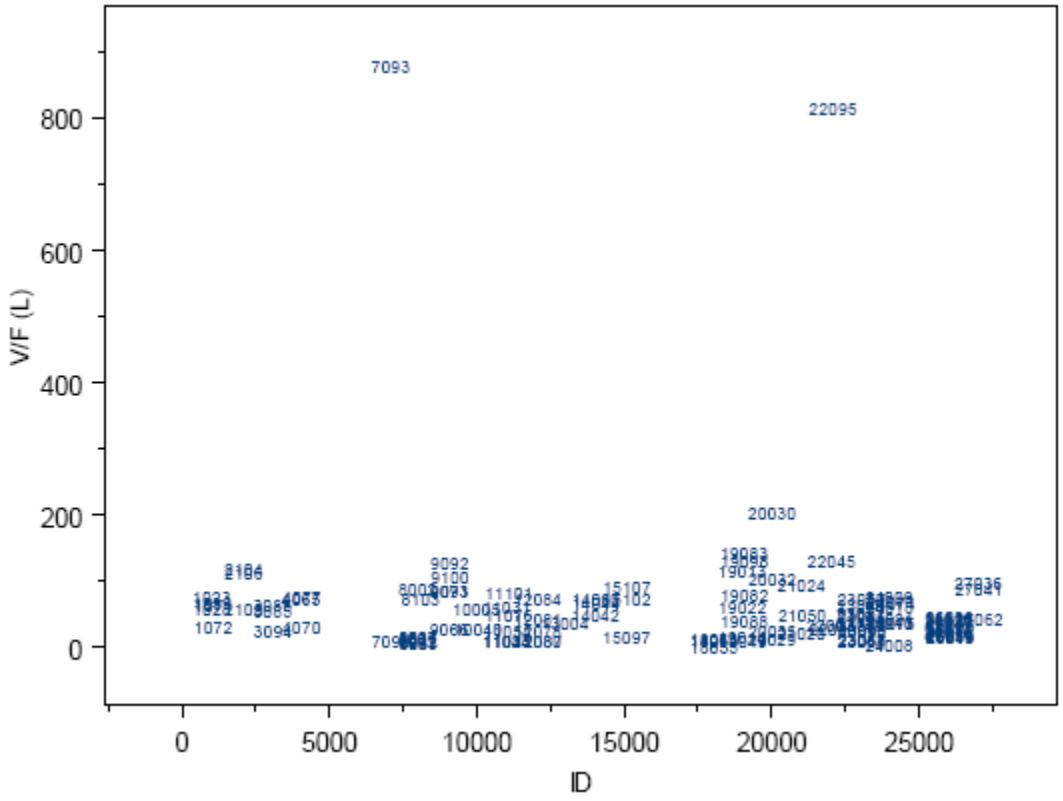


Table P2 Population Pharmacokinetic Parameter Estimates for PegIntron with Subjects 7093 and 22095 Excluded

Parameters	Estimate (%SE)	Inter-individual variability (%SE)
CL/F (L/hr)	0.664 (10)	32.6% (56)
V/F (L)	42.4 (11)	35.9% (84)
Ka (1/hr)	0.0882 (19)	34.2% (168)
Covariates	**Estimated Effect (%SE)**	
Age on CL/F	1.21 (18)	
Sex on CL/F	1.09 (16)	
Age on V/F	1.44 (0.2)	

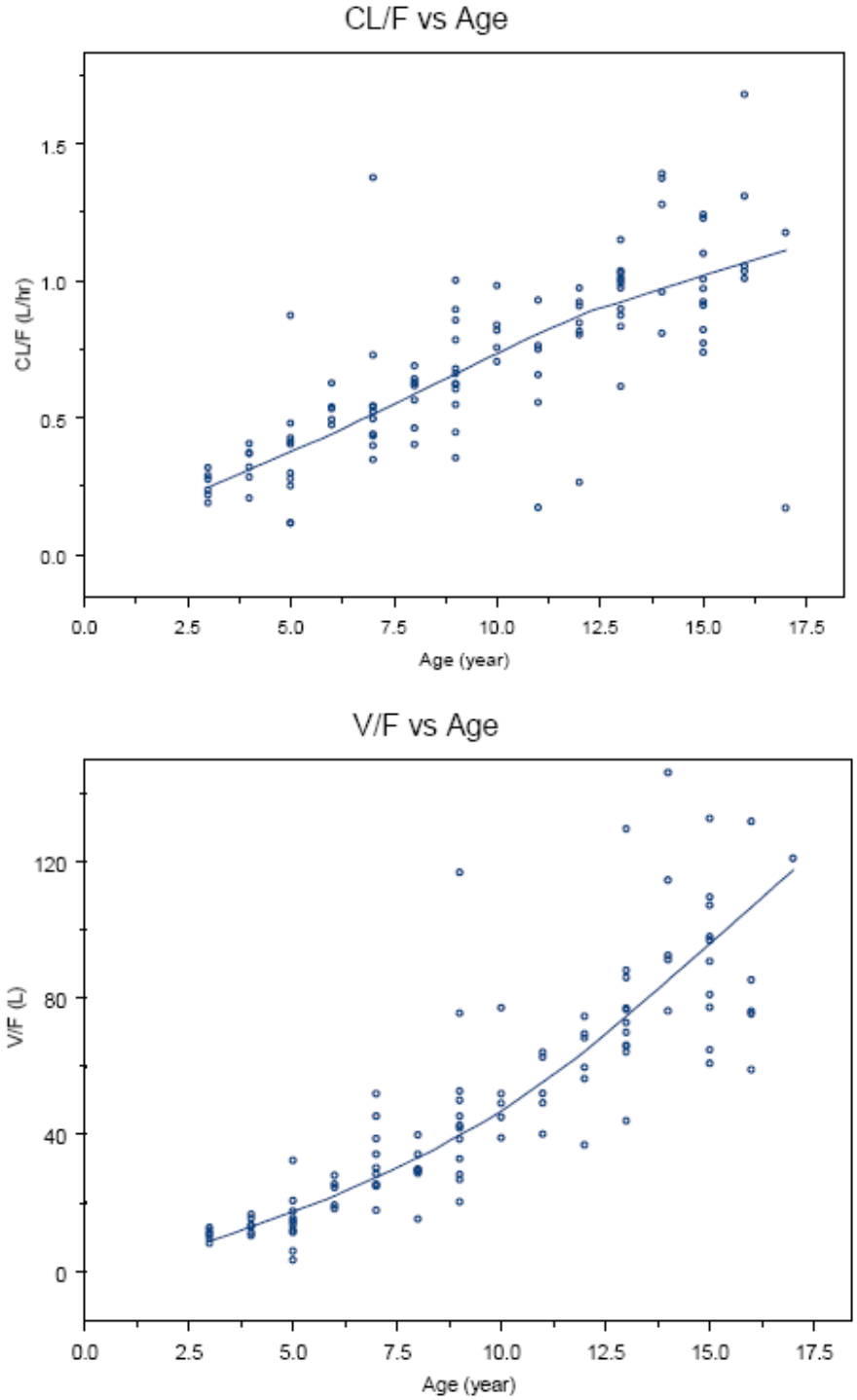
Residual variability		
Proportional error	37.7% (23)	
Additive error (pg/mL)	120 (31)	

CL/F = apparent clearance; Ka = first order absorption rate constant; SE = standard error; V/F = apparent volume of distribution.

Compared with parameters presented in Table P1, Table P2 suggested that exclusion of two male Subjects 7093 and 22095 had made the effect of sex on CL/F much less (9% vs. 27% when these two subjects were included). Therefore, sex is not expected to make clinically significant effect on PegIntron PK, and is not subject to dose changes. For other pharmacokinetic parameters, the effect of excluding Subjects 17093 and 22095 is minimal.

As shown in Figure P4, the apparent clearance (not body size adjusted) and the volume of distribution of PegIntron are increased with age.

Figure P4 Correlation between CL/F of Peg-Intron and Age (Upper Panel) or between V/F of Peg-Intron and Age (Bottom Panel) from final model



Line fit: loess smooth line

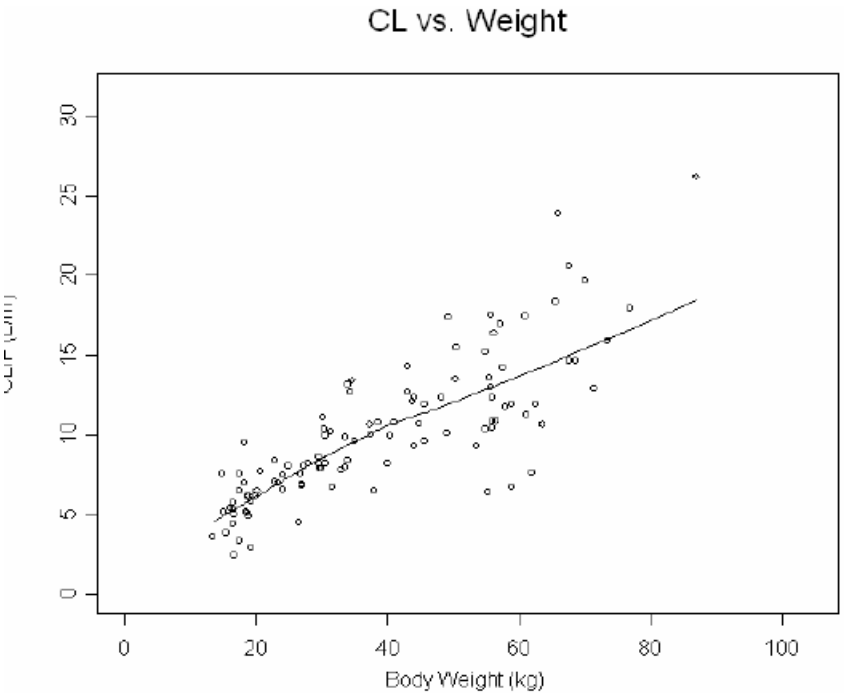
Ribavirin

All pediatric subjects dosed with ribavirin with at least one measurable plasma ribavirin concentration were included in the analysis (N=107). A total of 726 concentration measurements were used in the population pharmacokinetic analysis.

First order conditional estimation method (FOCE) with interaction (INTERACTION) was used for the analysis of plasma ribavirin concentrations. Both a one compartment model and a two compartment model were evaluated as base model. The two compartment model was found to be superior to the one compartment model based on the objective function value (OFV) and goodness of fit plots. A two compartment model with first order absorption, exponential inter-individual variabilities on clearance, volume of distribution of central and peripheral compartments, distributional clearance, and with a proportional residual error model was identified as base model.

Covariates were investigated using a two-stage approach or using a stepwise generalized additive modeling (GAM) procedure. Baseline body weight, height, body surface area, body mass index, race, sex, serum creatinine level, creatinine clearance, serum ALT levels were tested as potential covariates during model building process. If a simple covariate candidate, e.g., body weight, reduced the OFV to a similar level as derived compound covariate candidate, e.g., BSA, the simple covariate candidate was preferred. As shown in Figure P1, covariates body weight, height, age and body surface area correlated with each other. Among those correlated covariates, body weight has been shown to be the most significant covariate for CL/F, apparent volume of distribution of the central compartment (Vic/F); peripheral volume of distribution (Up/F), and apparent distributional clearance (Q/F). Figure P5 shows Ribavirin CL/F is increased with Body Weight for Pediatric Subjects.

Figure P5 Correlation between CL/F of Ribavirin and Body Weight for Pediatric Subjects from final model



The final model is a two compartment model with first order absorption, exponential inter-individual variabilities on clearance, volume of distribution of central and peripheral compartments, distributional clearance, and with covariate effect of body weight on clearance, the central volume of distribution, peripheral volume of distribution and distributional clearance, and with a proportional residual error model. The final population pharmacokinetic parameters of ribavirin are included in Table P3.

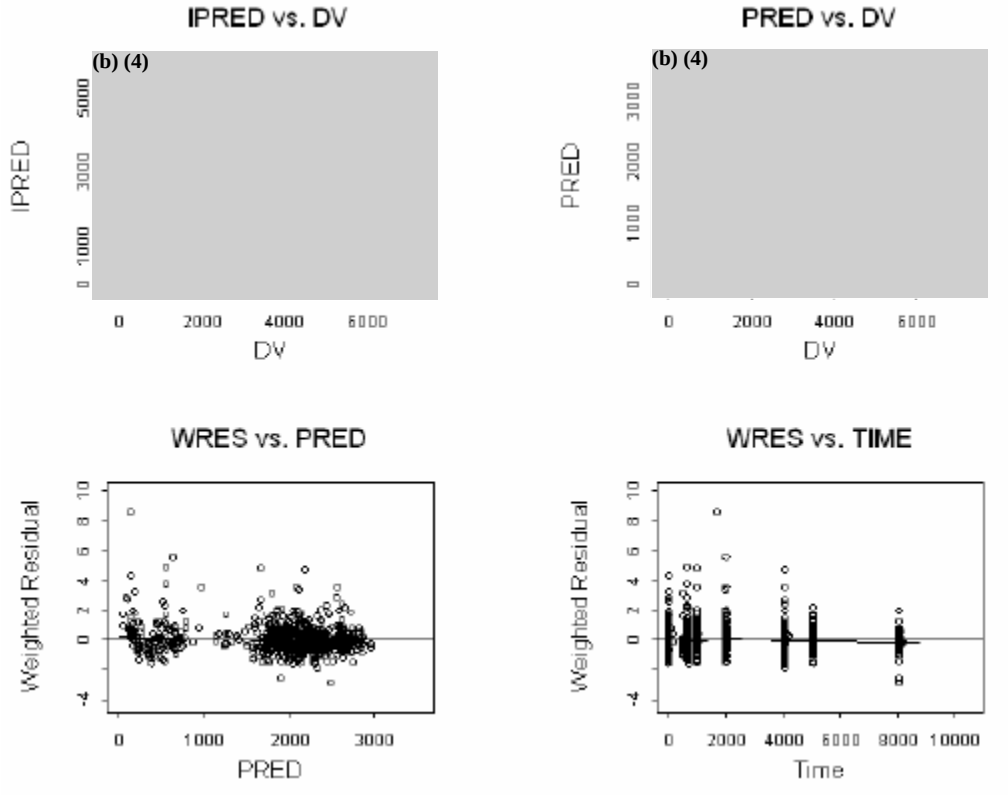
Table P3 Population Pharmacokinetic Parameter Estimates for Ribavirin

Parameters	**Estimate (%SE)**	**Inter-individual variability (%SE)**
CL/F (L/hr)	10.1 (2.8)	24.5% (19.4)
Vc /F(L)	74.9 (18.6)	72.2% (42)
Vp/F(L)	1720 (14)	69.5% (25.3)
Q/F (L/hr)	63.6 (8.2)	40% (49.8)
Ka (1/hr)	0.31 (fixed)	
Covariates	**Estimated Effect (%SE)**	
Body Weight on CL/F	0.838 (7.4)	
Body Weight on Vc/F	1.88 (23.1)	
Body Weight on Vp/F	1.09 (14.8)	
Body Weight on Q/F	0.799 (17)	
Residual variability		
Proportional error	22.7% (13)	

CL/F = apparent clearance; Ka = first order absorption rate constant; SE = standard error; Q/F = apparent distributional clearance; Vc/F = apparent volume of distribution of the central compartment; Vp/F = apparent volume of distribution of the peripheral compartment.

Goodness-of-fit plots for the final pharmacokinetic model are presented in Figure P6. The individual predicted vs. observed plasma ribavirin concentrations were scattered around the line of unity. The weighted residuals did not show any major trend when plotted over sampling time or population predicted value, suggesting that the model was unbiased.

Figure P6: Goodness of Fit Plots for the Final Population Pharmacokinetic Model of Ribavirin: individual predicted concentrations vs. observed concentrations (upper left); population predicted concentrations vs. observed concentrations (upper right); weighted residuals vs. population predicted concentrations (bottom left); weighted residuals vs. time (bottom right).



Reviewer's Analysis

Introduction

The purpose of the population PK analysis in this submission is to compare the PegIntron and ribavirin exposures in pediatric subjects with the values obtained at approved doses for adults and/or pediatric patients. Additional graphs were made to compare the PK parameters of pediatrics with adults to make sure proposed dosing regimens are appropriate. In addition, body weight based regimen for PegIntron was also explored to check if we can simplify PegIntron regimen, because body weight based regimen is used in adults for PegIntron and is used for both adults and pediatrics for ribavirin. Some simple checks of model performance were also conducted to ensure the appropriateness of the models.

Objectives

- Check model performance
- Examine if the applicant's proposed dosing regimens are appropriate

Methods

Data Sets

Data sets used are summarized in Table P4.

Table P4 Analysis Data Sets

Study Number	Name	Link to EDR
P02538	2538e.csv	\\cbsap58\M\eCTD_Submissions\STN103949\0000\m5\datasets\p02538\analysis\program
	P02538ribanm.csv	\\cbsap58\M\eCTD_Submissions\STN103949\0000\m5\datasets\p02538\analysis\program

Software

NONMEM was used in the population pharmacokinetic analysis. Excel and S-plus were used for data manipulation and plots.

Models

The sponsor's final model was used.

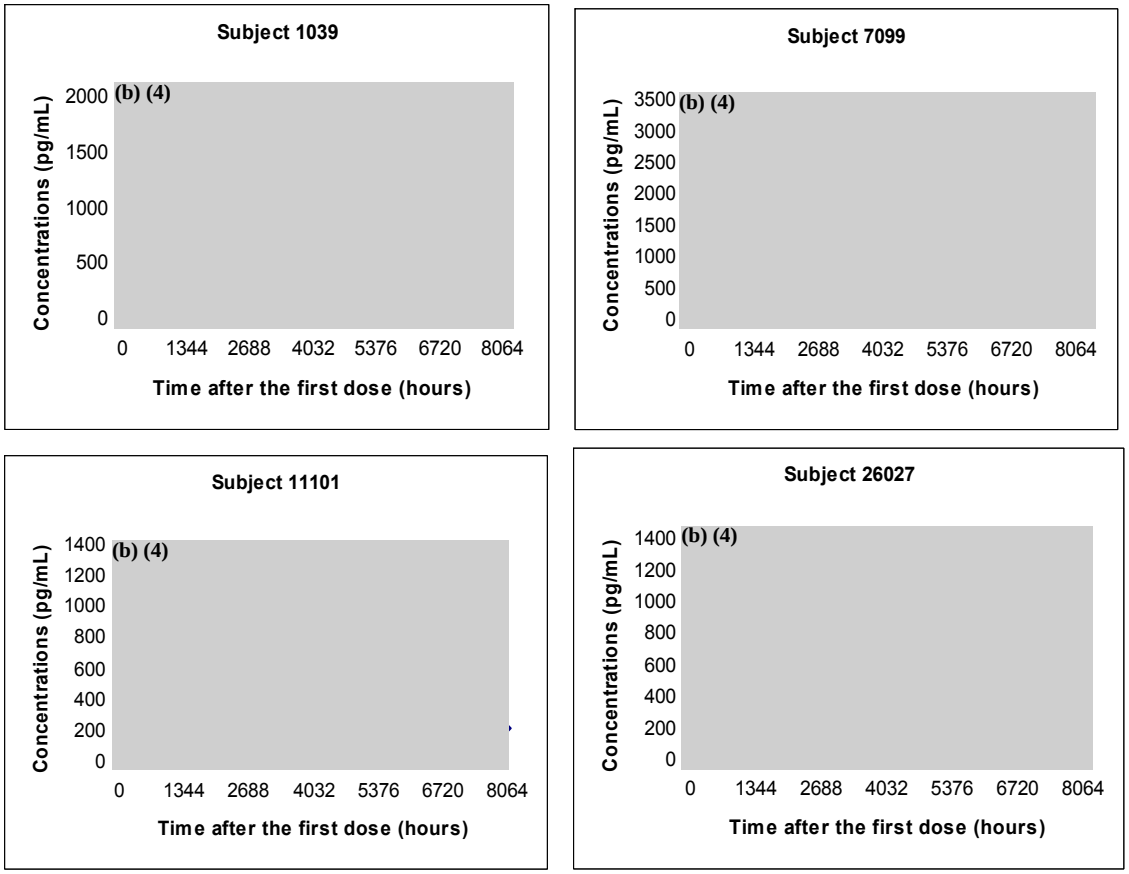
Results

PegIntron (PEG2b)

Linear PK model has been used in the analysis for pediatric subjects. However, in adults, the apparent clearance (CL/F) for PEG2b was decreased from 25.0 mL/hr/kg at Week 1 to 18.5 mL/hr/kg at Week 4 at dose of 1.5 µg/kg/week. The population pharmacokinetic analysis (Jen, F et. al, 2001) indicated that the apparent clearance continued to decline by 33.7% from Week 4 to Week 48 in adults. We examined the appropriateness of using linear PK model in pediatric subjects. As shown in Figure P2, the weighted residuals did not show any major trend when plotted over sampling time, suggesting the linear model generally fits the data. In addition, individual concentrations vs. time after the first dose were plotted for each subjects. The predicted concentrations generally agree with the observed concentrations. Figure P7 shows some examples of the individual plots.

The data from limited non-compartmental analysis (NCA) indicated the exposures obtained from NCA are generally agreed with the results from population PK analysis. See Pediatric Study Clinical Pharmacology Review for details.

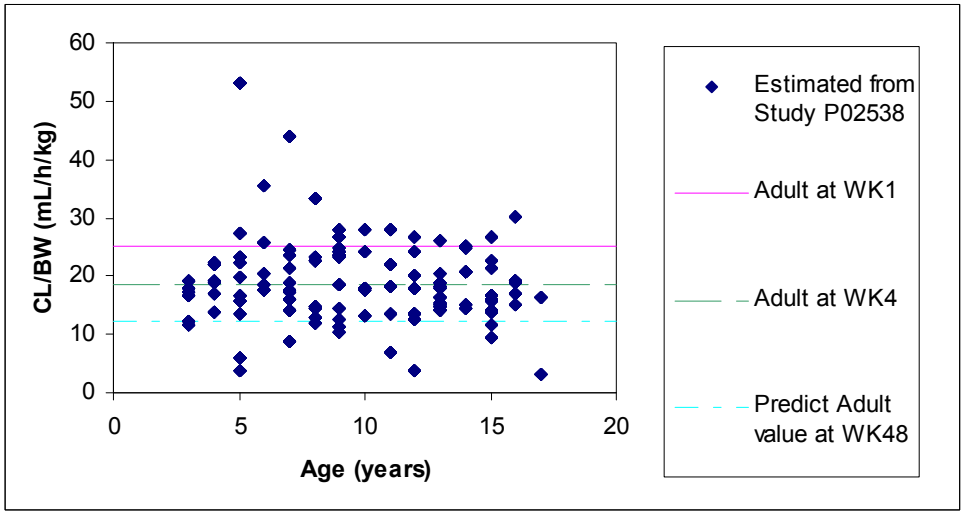
Figure P7 Examples of PEG2b individual predicted concentrations (solid lines) as compared to observed concentrations (dots)



The dose of PEG2b used for study P02538, 60 µg/m^2 QW, is approximately equivalent to the dose approved for adults, 1.5 µg/kg QW, based on calculated conversion to body surface area (BSA).

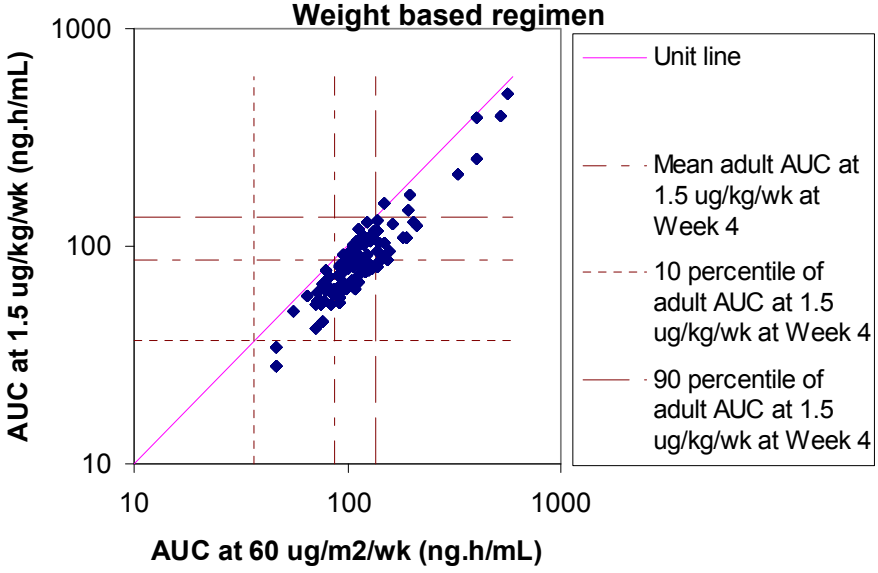
Because only body weight normalized clearance was reported for PEG2b in adults, the body weight normalized apparent clearances were estimated in pediatric subjects. As shown in Figure P8, the body weight normalized apparent clearances in pediatric subjects are within the range of the observed values in the adults. Therefore, if the pediatric subjects take the same dose as adults (1.5 µg/kg/week), the PEG2b AUC in pediatric subjects should be similar to the values observed in adults.

Figure P8 The comparison of body weight normalized apparent clearance of PEG2b between pediatric subjects in Study P02538 and adults from historical data



Because body weight (BW) based regimen is used in adults for PEG2b and is used for both adults and pediatrics for ribavirin; in addition, 1.5 µg/kg/week PEG2b in pediatric subjects may provide similar exposures as compared to the achieved level in adults at approved dose, BW based regimen for PegIntron was also explored to check if it can provide similar exposure as proposed body surface area (BSA) based regimen (the regimen studied in P02538). As shown in Figure P9, the PEG2b AUCs for BW based regimen at 1.5 µg/kg/week are somewhat lower than the values obtained based on the body surface area (BSA, 60 µg/m^2/week). Only AUC was compared, because the Cmax of PEG2b can not be accurately estimated from the sparse samples in Study P02538.

Figure P9 PEG2b AUC Correlation between Body Surface Area based or Body Weight based regimen



In pediatric subjects receiving BSA based dosing of PEG2b at 60 µg/m^2/week, the log-transformed ratio estimate of exposure during the dosing interval is predicted to be approximately 50% higher than observed in adults receiving 1.5 µg/kg at Week 4 (Table

P5). However, because PEG2b exposure increase with time and the exposure collected in this study is from Week 1 to Week 48, the exposure comparison here only serving as a rough comparison. Because BW based regimen at 1.5 µg/kg/week would provide exposure lower than the BSA based regimen at 60 µg/m^2/week, and the efficacy and safety data support the studied BSA based regimen (see QBR A5), the higher BW normalized dose than adults should be used to achieve the exposures of 60 µg/m^2/week in pediatric patients. Although BW based regimen may provide simpler regimen than BSA based regimen, the Medical Officer indicated BSA based regimen has been used for interferons for other indications. Therefore, **the applicant's proposed BSA based dosing regimen 60 µg/m^2/week for PEG2b in pediatric patients at least 3 years old is acceptable.**

Table P5 Predicted mean (%CV) AUC(τ) of PEG2b in Pediatric Subjects as compared to adults at Week 4

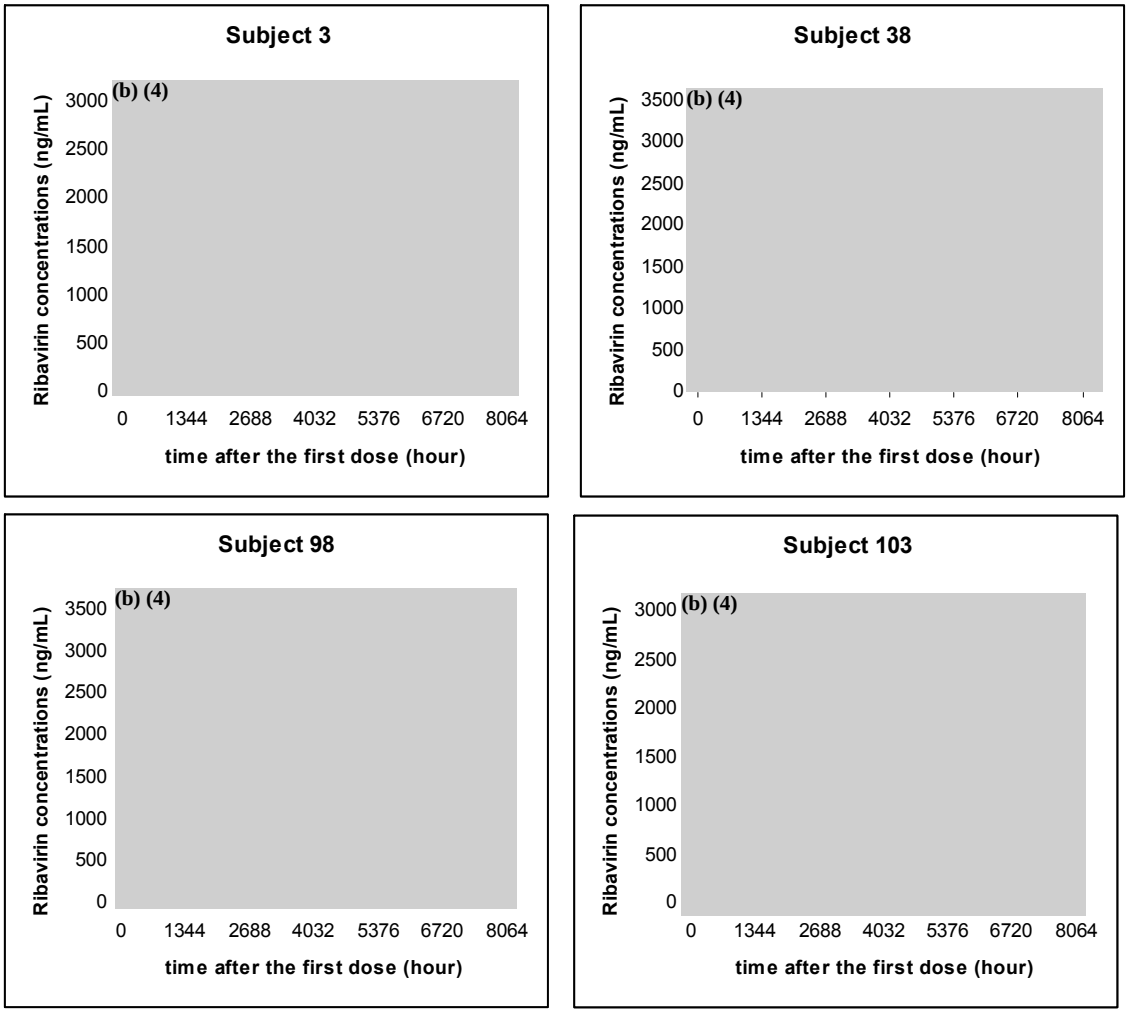
	PEG2b	
Dose	1.5 µg/kg in Adult Subjects	60 µg/m^2/wk in Pediatric Subjects
Study/Source	P02927 & I95-060	P02538
n	22 [c]	107
AUC(τ) mean (%CV)	71100 (36)	127000 (63)
AUC(τ) LS mean [a]	67700	107000[b]
AUC(τ) Ratio (90% CI): Pediatric vs Adult	1.58 (1.41-1.77)[b]	

CV% = coefficient of variation in percent; n = the number of subjects
AUC(τ) (pg·hr/mL) for PEG2b: τ =168 hr
a: Model-based (least squares) mean: ANOVA extracting the effects due to subject type
b: n=102for P02538. Subjects 7093, 18055, 20030, 22095, 24008 from P02538 were excluded due to statistical outlier; AUC geometric mean is 114500 pg.hr/mL including these 5 subjects
c: n=6 for I95-060 and n=16 for P02927
ANOVA = analysis of variance; CI = confidence interval; LS mean= least-square mean; NA = not applicable

Ribavirin

As shown in Figure P6, the goodness-of-fit plots for ribavirin in the final pharmacokinetic model show that the model was appropriately unbiased. Individual concentrations of ribavirin vs. time after the first dose were plotted for each subject. The predicted concentrations generally agree with the observed concentrations. Figure P10 shows some examples of the individual plots.

Figure P10 Examples of ribavirin individual predicted concentrations (solid lines) as compared to observed concentrations (dots)



The body weight normalized apparent clearance of ribavirin is similar across the pediatric age groups and similar to those reported in a prior study of ribavirin in combination with Intron A and in adult patients (Figure P11). For pediatrics, the approved dose of ribavirin is 15 mg/kg per day (divided dose AM and PM) orally in combination with Intron A. The Cmax of ribavirin can not be accurately estimated from Study P02538, because of the sparse sampling from the study. Therefore, only AUC was compared. As shown in Table P6, the AUCτ of ribavirin in pediatric subjects from Study P02538 and the previous study of ribavirin in combination with Intron A. Therefore, the applicant's proposed body weight based regimen of ribavirin 15 mg/kg/day is acceptable.

Figure P11: The comparison of body weight normalized apparent clearance of ribavirin between pediatric subjects in Study P02538 and the values observed in previous pediatric and adult studies

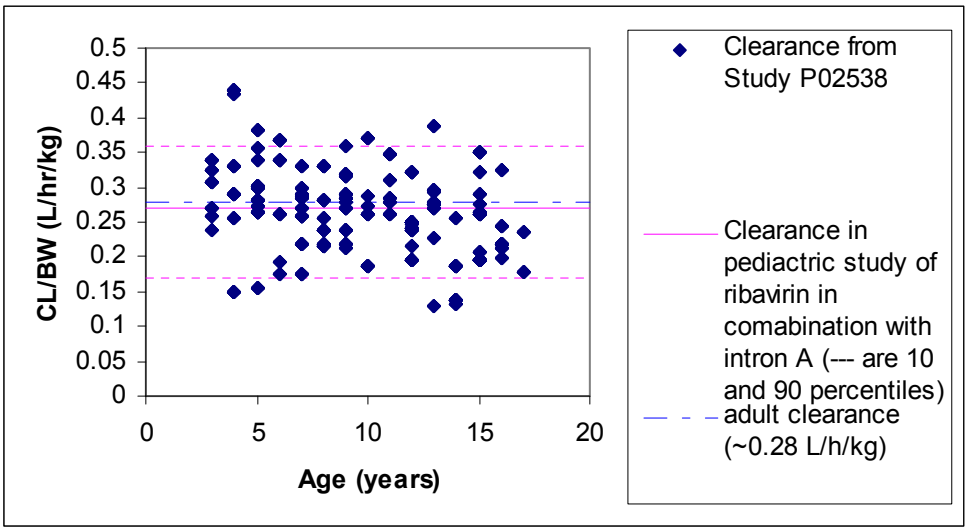


Table P6 Across study comparison of mean (%CV) AUC(τ) of ribavirin in pediatric subjects

	Ribavirin	
Dose	15 mg/kg/day as 2 divided doses in Pediatric Subjects	
Study/Source	P02538	Product Information
n	107	17
AUC(τ) mean (%CV)	29100 (25)	29774 (26)
AUC(τ) LS mean [a]	28300	NA
AUC(τ) Ratio (90% CI): Pediatric vs Adult	NA	

CV% = coefficient of variation in percent; n = the number of subjects
AUC(τ) (ng·hr/mL) for ribavirin: τ =12 hr
a: Model-based (least squares) mean: ANOVA extracting the effects due to subject type

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